Drug Interactions

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Drug Interactions: Definition

" The pharmacologic or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two agents when given alone [1] "

[1]Tatro DS (Ed.) Drug Interaction Facts. J.B. Lippincott Co. St. Louis 1992.

Epidemiology of Drug-Drug Interactions

- True incidence
  - Difficult to evaluate due to underlying disease
  - Data for drug-related hospital admissions focus on ADRs
- Risks
  - Elderly
  - Polypharmacy
  - Patients receiving less common and/or OTC medications
- Potential Repercussions
  - Patient injury up to and including death
  - Disease progression
  - Lost wages
  - Health care costs

Types of Drug Interactions

- **Pharmacokinetic**
  - What the body does with the drug
  - One drug alters the concentration of another by altering its absorption, distribution, metabolism, or excretion
  - *Usually* (but not always) mediated by cytochrome P450 (CYP)
- **Pharmacodynamic**
  - Related to the drug's effects in the body
  - One drug modulates the pharmacologic effect of another: additive, synergistic, or antagonistic

Pharmacodynamic Drug Interactions

- **Synergistic combinations**
  - Pharmacologic effect > than the summation of the 2 drugs
  - Beneficial: aminoglycoside + penicillin
  - Harmful: barbiturates + alcohol
- **Antagonism**
  - Pharmacologic effect < than the summation of the 2 drugs
  - Beneficial: naloxone in opiate overdose
  - Harmful: zidovudine + stavudine
- **Additivity**
  - Pharmacologic effect = than the summation of the 2 drugs
  - Beneficial: aspirin + acetaminophen
  - Harmful: neutropenia with zidovudine + ganciclovir

Pharmacodynamic Drug Interactions

- Idiosyncratic (Type B drug interactions)
  - Occur rarely and unpredictably
  - The reaction is not a simple extension of the drug's pharmacologic activity; usually immune mediated
  - Example: meperidine + MAO inhibitor

Concurrent use of meperidine and MAO inhibitors may result in hypertensive crisis, hyperpyrexia and cardiovascular system collapse, and may be fatal.

Pharmacokinetic Drug Interactions

Absorption: G.I. motility, pH, chelate formation

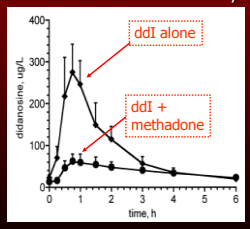
Distribution: transport proteins; penetration into sanctuary sites, plasma protein binding

Metabolism: Phase I (CYP450)
Phase II (conjugation)

Elimination: Renal (glomerular filtration; tubular secretion)

Alterations in Absorption: GI Motility

Decreased GI motility via methadone increases didanosine (ddI) degradation and reduces ddI bioavailability



J Acquir Immune Defic Syndr. 2000;24:241-8.

Increased GI motility by metoclopramide reduces digoxin absorption

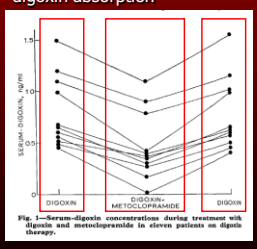


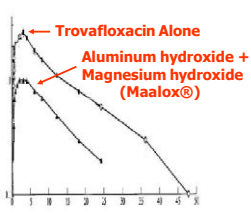
Fig. 1—Serum-digoxin concentrations during treatment with digoxin and metoclopramide in eleven patients on digoxin therapy.

Lancet 1973;1:398-400.

Alterations in Absorption: Chelation

- Definition:
  - Irreversible binding of a drug in the GI tract
  - Tetracyclines, quinolone antibiotics + ferrous sulfate (Fe^{+2}), antacids (Al^{+3}, Ca^{+2}, Mg^{+2}), dairy products (Ca^{+2})
  - Usually separating administration of chelating drugs by 2+ hours decreases interaction effect

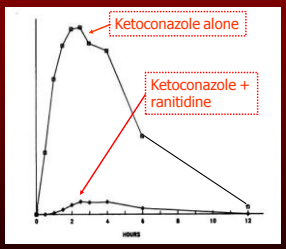
Trovafloxacin +/- Maalox®



J Antimicrob Chemother. 1997 Jun;39 Suppl B:93-7.

Alterations in Absorption: pH

- Some drugs require an acidic environment for optimal absorption in the GI tract
- Examples: atazanavir, itraconazole, & ketoconazole. H2 blockers and PPIs reduce absorption of these drugs

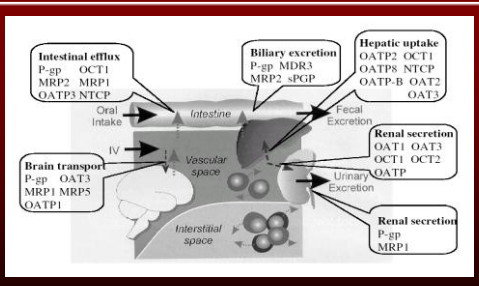


Antimicrob Agents Chemother. 1991 Sep;35(9):1765-71.

Alterations in Absorption: anion exchange resins

- Anion exchange resins (i.e. cholestyramine)
  - Form insoluble complexes & ↓ drug absorption
    - Warfarin, digoxin, β-blockers, NSAIDS, others?
    - Immunosuppressants?
      - Cholestyramine sometimes used to TX *Clostridium difficile* colitis
      - Interaction could result in ↓ immunosuppressant absorption and possible graft failure in transplant recipients
  - Stagger dose of exchange resin with other meds
    - Difficult due to multiple daily dosing of cholestyramine

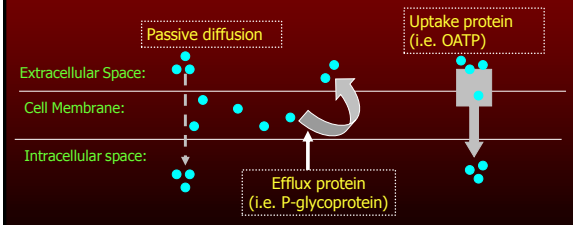
Drug Interactions: Transport Proteins



Ayrton A, Morgan P. Role of transport proteins in drug absorption, distribution and excretion. Xenobiotica. 2001;31:469-97.

Drug Transport Proteins

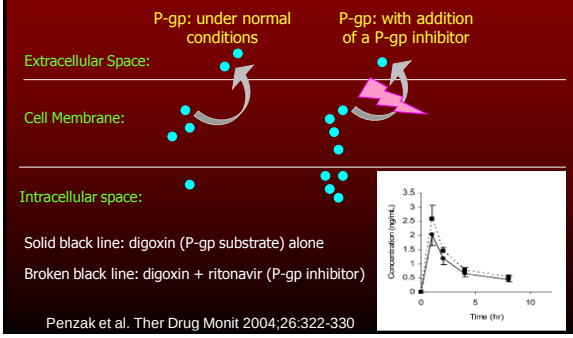
- Transport Proteins
  - Efflux: extrudes drugs outside of cell
  - Uptake: facilitates intracellular movement of molecules



Drug Transport: Efflux

- Efflux proteins: focus on P-gp (ABCB1)
  - An ATP binding cassette protein (ABC); MDR1 gene product
  - Originally identified in MDR cancer cells
  - Located in GI tract, BBB, liver, kidney, lymphocytes etc.
  - Transports many chemically diverse compounds
  - May affect ADME of substrates (i.e. drugs)
  - Modulation of P-gp by one drug may alter the PK of another
  - Substrates: digoxin, colchicine, fexofenadine, talinolol
  - Inhibitors: cyclosporine, verapamil, erythromycin, itraconazole
  - Inducers: phenobarbital, rifampin, phenytoin, St. John's wort

Drug Transport: Inhibition of Efflux



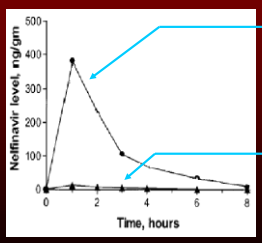
Solid black line: digoxin (P-gp substrate) alone

Broken black line: digoxin + ritonavir (P-gp inhibitor)

Penzak et al. Ther Drug Monit 2004;26:322-330

Drug Transport: Preventing accumulation in a sanctuary site: brain tissue

- **^{14}C Nelfinavir +/- LY-335979 in *MDR1a* wild type Mice**



● Tissue ^{14}C NFV conc. in brain
^{14}C NFV + LY-335979 (P-gp inhibitor)

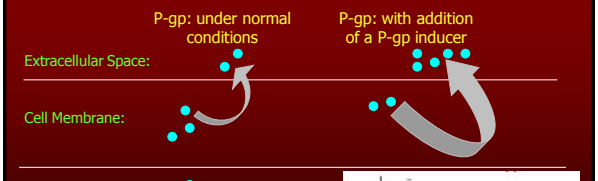
Significant accumulation of ^{14}C NFV due to inhibition of P-gp-mediated ^{14}C NFV efflux

▲ Tissue ^{14}C NFV conc. in brain
^{14}C NFV + vehicle

Minimal accumulation of ^{14}C NFV due to P-gp-mediated efflux

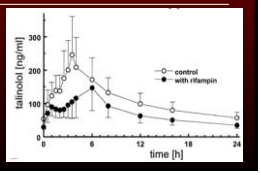
Choo EF et al. Drug Metab Disposit 2000;28:655-660.

Drug Transport: Induction of Efflux



Open circles: talinolol (P-gp substrate) alone

Filled circles: talinolol + rifampin (P-gp inducer)



Clin Pharmacol Ther 2000;68:345-55.

Drug Transport: Uptake

- Uptake proteins: focus on OATP (also OCT, OAT)
  - Transport numerous amphipathic compounds
  - Some present only in the liver
  - Many present at the BBB, lung, heart, intestine, kidney etc.
  - Facilitate the influx of compounds
  - Fexofenadine and digoxin are well-defined OATP substrates
  - Fruit juices inhibit OATPs, along with quinidine, nelfinavir, saquinavir, and ketoconazole

Drug Transport: Uptake in the G.I. tract

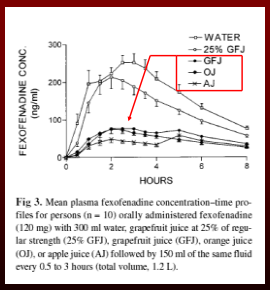
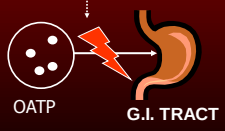


Fig 3. Mean plasma fexofenadine concentration–time profiles for persons (n = 10) orally administered fexofenadine (120 mg) with 300 ml water, grapefruit juice at 25% of regular strength (25% GFJ), grapefruit juice (GFJ), orange juice (OJ), or apple juice (AJ) followed by 150 ml of the same fluid every 0.5 to 3 hours (total volume, 1.2 L).

Fruit juices (grapefruit juice, apple juice, and orange juice) inhibit OATP and reduce fexofenadine absorption



Clin Pharmacol Ther. 2002 Jan;71(1):11-20.

Drug Transport: Uptake into the liver

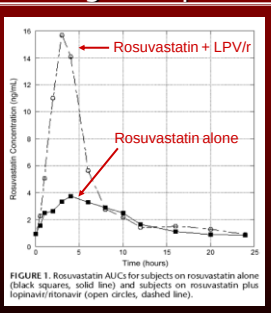
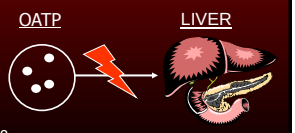


FIGURE 1. Rosuvastatin AUCs for subjects on rosuvastatin alone (black squares, solid line) and subjects on rosuvastatin plus lopinavir/ritonavir (open circles, dashed line).

- OATP 1B1 uptakes drug into the hepatocyte where it then undergoes subsequent metabolism.
- Blockade of OATP 1B1 (by LPV/r) results in reduced metabolism and increased plasma drug (rosuvastatin) concentrations



J Acquir Immune Defic Syndr. 2008;47:570-8

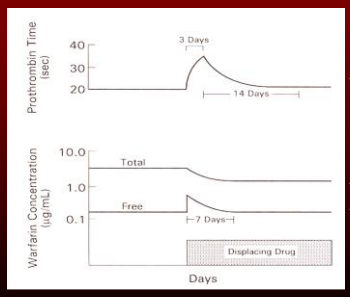
Distribution: Protein Binding Interactions

- Non-restrictively cleared drugs
  - Eliminating organ removing most of the drug being presented to it, including the fraction bound to plasma proteins
  - Increase in fu will not lead to a proportional increase in CL
  - No examples of clinically significant protein binding interactions have been identified with non-restrictively cleared drugs

Distribution: Protein Binding Interactions

- Restrictively cleared drugs
  - Small fraction of drug extracted during single passage through the eliminating organ ($E \leq f_{ub}$)
  - *Only unbound drug in plasma can be cleared*
  - Increase in f_u leads to proportional increase in total drug CL and decrease in total drug Cpss
  - $Cpss_{ub}$ will return to pre-displacement value after transient increase
    - Only likely to clinically significant for drugs with LONG T ½, SMALL Vd, narrow therapeutic range, ↑ PPB
    - Example: warfarin displacement from serum albumin by a metabolite of chloral hydrate (trichloroacetic acid)

Distribution: Protein Binding Interactions



↑ in warfarin pharmacodynamic effect

Total drug conc. decreases

↑ in free drug conc.
↑ in Cl_{int}
Free drug conc. returns
To predisplacement level

Displacing drug added (TCAA + warfarin)

Principles of Clinical Pharmacology, pg 64

Distribution: Protein Binding Interactions

"…the overall clinical importance of plasma protein binding displacement interactions continues to be overstated…"

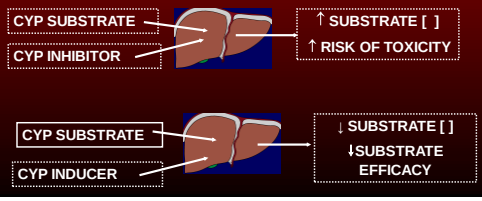
" Despite the theoretical and experimental data to the contrary, the concept that plasma protein binding displacement is a common cause of clinically significant interactions may still be widely taught in some medical schools, often appears in textbooks and is accepted by many in the medical community and by drug regulators."

Sansom LN & Evans AM. Drug Safety 1995;12:227-233.
Rolan PE. Br J Clin Pharmacol 1994;37:125-128.

Drug Metabolism Interactions

Typically occur in the liver and/or G.I. tract

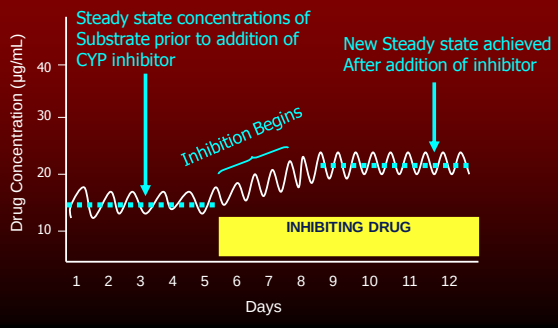
Inhibition or induction of CYP enzymes by one drug that results in altered metabolism (and systemic exposure) of another coadministered medication



Drug Metabolism Interactions: Inhibition

- Usually by competitive binding to enzyme site
- Typically occurs quickly; depends on the time to steady-state of the inhibitor
- Time to maximum interaction effect dependent on time required for substrate drug to reach new steady-state
- Mechanism-based enzyme inactivation
  - Grapefruit juice and intestinal CYP3A content
  - Duration depends on time needed to restore active enzyme

Drug Metabolism Interactions: Inhibition



Drug Metabolism Interactions: Inhibition

- May be metabolized one or more CYP enzymes

↑↑ Desipramine → 2D6
↑↑ Phenytoin → 2C9
↑↑ Midazolam → 3A4/5
↑↑ Caffeine → 1A2
↑↑ Omeprazole → 2C19

Enzyme inhibition results in significant increases in the substrate medication

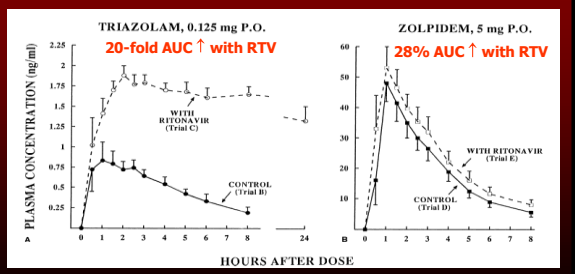
Voriconazole → 2C9, 2C19, 3A4
Efavirenz → 3A4, 2B6
Amitiptyline → 1A2, 2C9, 2C19, 2D6

Inhibition of one enzyme may be offset by the ability of other enzymes to "pick up the slack"

Drug Metabolism Interactions: Inhibition

TRIAZOLAM: 100% metabolized by CYP3A

ZOLPIDEM: 60% metabolized by CYP3A 40% by other CYPs



Greenblatt et al. J Acquir Immune Defic Syndr. 2000 Jun 1;24(2):129-36.

Drug Metabolism Interactions: Inhibition

- Some Examples of strong* inhibitors
  - CYP1A2: ciprofloxacin; fluvoxamine
  - CYP2C8: gemfibrozil
  - CYP2C9: fluconazole
  - CYP2C19: omeprazole, rebeprazole, lansoprazole
  - CYP2D6: fluoxetine
  - CYP3A: itraconazole, ketoconazole, HIV protease inhibitors, clarithromycin

* 5-fold ↑ in substrate AUC or 80% ↓ substrate clearance

http://medicine.iupui.edu/flockhart/table.htm

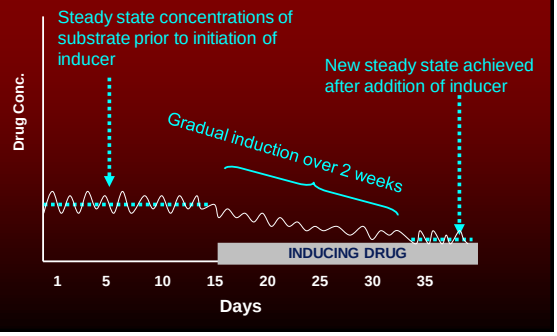
Drug Metabolism Interactions: Inhibition

- Key questions when assessing potential inhibition INX:
  - What is the safety index of the substrate medication?
    - ➢Can a small ↑ in conc. result in toxicity (digoxin; tacrolimus)
    - ➢Can relatively large ↑s in conc. be well-tolerated? (SSRIs)
  - Is the substrate metabolized by one, or multiple CYPs?
  - Does the substrate have active metabolites?
    - ➢Can pro-drugs form the active metabolite?
      - ✓Clopidogrel + CYP2C19 inhibitor (i.e. omeprazole)
        - The thiol active metabolite isn't formed resulting in reduced pharmacologic (antiplatelet) activity

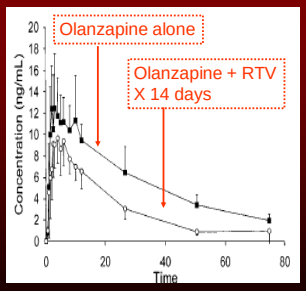
Drug Metabolism Interactions: Induction

- Gradual onset and offset
  - Involves increased DNA transcription and synthesis of new CYP enzymes –this takes time
- Onset and offset
  - Depends on T ½ of inducer, time to make new CYP proteins, and rate of degradation of CYP proteins
- Results in reduction of plasma concentration of substrate drugs
  - Risk of therapeutic failure
  - Induction may lead to formation of toxic metabolite
  - Removal of inducer may lead to toxic concentrations of substrate

Drug Metabolism Interactions: Induction



Drug Metabolism Interactions: Induction



Olanzapine is metabolized by CYP2D6 and UGT enzymes; BOTH of which are induced by ritonavir.

Penzak SR et al. J Clin Psychopharm 2002;22:366-70

Regulation of Drug Metabolism and Transport: Induction

- Nuclear Receptors (NR)
  - Function as modulators of gene expression
  - Ligand (drug, bile acid, hormone etc.) binds to vacant NR in the cytoplasm → enters the nucleus & forms homo or heterodimers which complexes to promotor/enhancer regions of target genes
    - Simply put: the gene is "switched on" (or off) causing it to produce (or not produce) mRNA and subsequent proteins
  - There are a number of nuclear receptors, some of which are involved in the regulation of multiple genes

Drug Metabolism Interactions: Induction

Target Gene	Nuclear Receptor	Ligands
CYP3A4	PXR, CAR, GR, HNF4α, VDR, FXR	PXR: rifampin, dexamethasone + others
CYP2C9	PXR, CAR, GR	CAR: phenobarbital
CYP2C19	CAR, GR	GR: dexamethasone
CYP2B6	PXR, CAR	
MDR1	PXR, CAR	
OATP8	FXR	FXR: chenodeoxycholic acid

Adapted from Urquhart et al J Clin Pharm 2007;47:566-78

Drug Metabolism Interactions: Induction

- Some examples of CYP inducers
  - 1A2: tobacco, cruciferous vegetables, omeprazole, ritonavir, modafinil, char-grilled meat
  - 2B6: phenobarbital, phenytoin, rifampin
  - 2C9: rifampin
  - 2C19: carbamazepine
  - 2D6: dexamethasone, rifampin
  - CYP3A: efavirenz, nevirapine, barbiturates, carbamazepine, rifampin, rifabutin, glucocorticoids, phenytoin, St. John's wort, troglitazone

http://medicine.iupui.edu/flockhart/table.htm

Predicting Drug Interactions: *in vitro* Screening

- Drug development: predicting *in vivo* drug interactions from *in vitro* data microsomes, hepatocytes, liver slices, purified CYP enzymes etc.
- Limitations and caveats
  - Most systems can only assess inhibition (not induction)
    - Some in vitro studies were later disproved in vivo
    - Hard to extrapolate data when drugs have multiple CYP pathways
    - In vitro conc. may not be physiologically relevant

Predicting Drug Interactions: CYP phenotyping

- Probe + putative inhibitor or inducer
- Usually conducted in healthy volunteers
- Typically administered as a multi-drug "cocktail"
  - Measure probe (+/- metabolite(s) concentration(s)
  - Examples of CYP probes
    - CYP1A2: caffeine
    - CYP2C9: tolbutamide; warfarin (+ vitamin K!)
    - CYP2C19: S-mephenytoin; omeprazole
    - CYP2E1: chlorzoxazone
    - CYP2D6: dextromethorphan; debrisoquine; sparteine
    - CYP3A4/5: midazolam, dextromethorphan, others
    - CYP3A4: erythromycin

Evaluating potential drug interactions in the clinical setting: points of consideration

- Is the interaction clinically significant
  - Therapeutic index of the "victim" drug
  - How many drugs potentially involved?
  - What is the likely time course of the interaction?
  - Is inhibition/induction a class effect?
    - Cimetidine vs. other H2 blockers
  - Options in managing the interaction
    - DC interacting drug, affected drug, or both?
    - Switch to another drug? -Same drug class or another?
    - Change dose of affected drug?
    - Add another drug to circumvent the interaction (i.e. RTV)?

Drug Interactions: General Tools for Evaluation and Management

- Familiarity with metabolic pathways
- Know where to locate information on interactions
- Obtain thorough medication HX at each visit
- Maintain high index of suspicion when:
  - Therapeutic response is less than expected
  - Toxic effects are present
- Choose drugs that are less likely to interact
- Consider TDM in certain situations
  - When multiple DDIs are suspected, pregnancy, children, other special populations (liver DZ etc.)

Drug Interactions: Resource examples

Site	Web Address
Micromedex[1]	www.micromedex.com
UCSF[2]	http://hivinsite.ucsf.edu/arvdb?page=ar-00-02&post=7
Indiana University Dave Flockhart table[3]	http://medicine.iupui.edu/clinpharm/ddis/table.asp
Natural Products Data Base[4]	http://www.naturaldatabase.com
Lexi-Comp Lexi-Interact[5]	www.lexi-comp.com

[1]Includes all drugs; paid subscription required
[2]Focus on HIV meds; free
[3]Exhaustive tables of CYP substrates, inhibitors, and inducers; free
[4]Focuses on natural prodcuts; paid subscription required
[4]Includes all drugs; paid subscription required

This is the end…